PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day month year)*	Priority date *(day/month/year)*
PCT/EP2004/007667	08.07.2004	10.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/20

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

VON EGGELKRAUT, S

Telephone No. +31 70 340-4732

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15 with respect to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 15 with respect to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-14,16
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1

1.1 Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claim 15 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2 Reference is made to the following documents:

D1: US-A-5 955 105 (AMIT K MITRA ET AL) 21 September 1999 (1999-09-21)
D2: US-A-5 958 979 (FRIESE ANDREA ET AL) 28 September 1999 (1999-09-28)

3 INDEPENDENT CLAIM 1

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claim 1 does not involve an inventive step in the sense of Article

33(3)PCT.

3.2 The document **D1** is regarded as being the closest prior art to the subject-matter of claim 1, and shows (the references in parentheses applying to this document): Stable tablets comprising levothyroxine sodium, microcrystalline sodium (80-95%), and croscarmellose sodium (0-5%) or starch (0-15% w/w) (c. 2, last par. - c. 3, par. 2; ex. 10). Croscarmellose sodium or starch are alternatives (c. 5, l. 58-60).

3.3 The subject-matter of claim 1 differs from this known composition in that the claimed formulation comprises microcrystalline cellulose of less than 125 micrometer and pregelatinised starch in an amount of 5-30% w/w.

3.4 The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

3.5 The problem to be solved by the present invention may be regarded as the provision of an alternative stable formulation of levothyroxine.

3.6 The solution to this problem proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: The composition of D1 solves the same problem and the solution provides the same advantages as the present invention. The particle size of microcrystalline cellulose seems to provide no further technical effect. D1 discloses starch as an alternative excipient. The selection of starch from a group consisting of two alternatives (croscarmellose sodium or starch), more specifically the use of pregelatinised starch, does not involve an inventive step, because said choice appears to be a matter of standard experimentation, because no technical effect seems to derive from said excipient. This even more as pregelatinised starch is disclosed in a stabilised levothyroxin formulation of document D2. D2 discloses stable tablets comprising levothyroxine sodium, pregelatinised starch and microcrystalline cellulose (D2, ex. 1, 2). The juxtaposition of technical features distinguishing the present invention from the prior art, without any further technical effect going beyond the disclosure of the prior art documents D1 and D2, does not involve an inventive step. Therefore, no inventive step can be acknowledged for claim 1.

3.7 INDEPENDENT CLAIMS 14-16

The above arguments apply, *mutatis mutandis*, to independent claims 14-16, which are also considered to lack an inventive step (Article 33(3) PCT).

4 DEPENDENT CLAIMS 2-13

Dependent claims 2-13 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).